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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,940	03/22/2004	Jean Deregnaucourt	PF114CIP	1022

25666 7590 02/07/2005

THE FIRM OF HUESCHEN AND SAGE
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KALAMAZOO, MI 49007

EXAMINER	
CHOI, FRANK I	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,940	DEREGNAUCOURT ET AL.	
	Examiner	Art Unit	
	Frank I Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 24-73 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 24-73 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/453,574.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 200400514.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement filed 5/14/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the Merck Index reference has no publication date. It has been placed in the application file and the information referred to therein has been considered as to the merits except for the Merck Index reference. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or

REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

A brief description of the drawings section entitled the same is required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment, does not reasonably provide enablement for prevention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The nature of the invention:

The claims are directed to methods of treating or prevention of various disorders with a mixture of enantiomers of milnacipran and/or of at least one of its metabolites, which is enriched with the (1S,2R) enantiomer.

The state of the prior art and the predictability or lack thereof in the art:

Although the prior art discloses treatment using the above there is no showing of prevention. As such, it appears that predictability in the art relative to prevention appears to be low.

The amount of direction or guidance present and the presence or absence of working examples:

The Specification does not appear to provide any examples showing prevention of any disease or condition.

The breadth of the claims and the quantity of experimentation needed:

The claims are broad in that they claim prevention of numerous conditions and disorders. As such, it appears that one of ordinary skill in the art would be required to do undue experimentation in order to determine whether a given condition or disorder will be prevented by administration of the active compounds above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kranzler et al. (US Pat. 6,602,911) in view of Rogosky et al. (US Pat. App. Pub. 2002/0010216), Spencer et al. (Drugs 1998), Tsuruta et al. (Abstract), Bonnaud et al.(J. Med. Chem. 1987) and Hirsh et al. (US Pat. App. Pub. 2004/0122104).

Kranzler et al. disclose methods of treatment of fibromyalgia, chronic fatigue syndrome, chronic pain and depression with mixtures of milnacipran enantiomers and that dextrogyral enantiomer is about twice as active and the racemic mixture and levrogyral enantiomer is much less potent (See entire document, especially, Column 6, lines 1-55). It is disclosed that the milnacipran can be administered adjunctively with other active compounds, such as antidepressants, such as tricyclic antidepressant and be in the form of a pharmaceutically acceptable salt with an inorganic acid such as hydrochloric acid (column 7, lines 45-65, column 9, lines 21-27). It is disclosed that the use of active metabolites is within the scope of the invention (Column 6, lines 56-60).

Rogosky et al. disclose methods of treatment of urinary incontinence, depression, phobias, stress induced problem with cardiovascular system, hypertension, chronic fatigue syndrome, fibromyalgia, pain disorder, addictive disorder and withdrawal syndrome, etc. with the combination of milnacipran and an antimucarinic agent (see entire document, especially, paragraphs 0010, 0030, 0034, 0035, 0043). It is disclosed that the combination provides rapid relief with a minimal amount of deleterious side effects (Paragraph 0045).

Spencer et al. disclose that the pharmacokinetics of milnacipran are not significantly effected by hepatic impairment and that the potential for drug interactions with drugs which are metabolized by the hepatic cytochrome system is reduced (Pg. 415). It is taught that, compared

with tricyclic antidepressants, milnaciprane had little effect on the cardiovascular system (Pgs. 413,414).

Tsuruta et al. disclose that the N-deethylated milnacipran is a metabolite of milnacipran (Abstract).

Bonnaud et al. disclose that N-deethylated milnacipran has antidepressant activity (Pgs. 319, 321 (Table II, No. 23), 322, 324).

Hirsh et al. disclose the use of milnacipran including metabolites including F2782 for treatment of depression and that the same can be combined with other active compounds such as antidpressants and antimuscarinics (Paragraphs 0017,0035, 0040 Claim 14).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose a treatment method using a mixture of enantiomers of milacipran and/or metabolites thereof, said mixture being enriched in the (1S, 2R) enantiomer. However, the prior art amply suggests the same as the prior art discloses that the dextrogyral enantiomer is the more effective of the enantiomers. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that the dextrogyral enantiomer, would be effective for the treatment of various diseases and conditions, including depression and urinary incontinence, can be combined with other drugs, such as antidepressants, such as tricyclic antidepressants, and antimuscarinic agents, with the expectation that the risk of cardiovascular disturbances and hepatic toxicities, including that caused by the co-administered drugs, would be reduced.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-28, 29-33, 35-53,55-58,60-73 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-67 of copending Application No. 10/453,574. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the present Application are anticipated by the above claims of 10/453,574 in that methods of limiting the risks of cardiovascular disturbances and/or the risks of organ and/or tissue toxicity in persons or animals having disorders which may be treated by double inhibition of serotonin and norepinephrine reuptake with the mixtures of enantiomers which are enriched with the dextro enantiomer, i.e. F2695 are claimed which is a species or embodiment of the claims of the present Application.

Claims 24-73 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 45-67 of copending

Application No. 10/453,574 in view of Kranzler et al. (US Pat. 6,602,911), Tsuruta et al. (Abstract), Bonnaud et al. and Hirsh et al. (US Pat. App. Pub. 2004/0122104).

Claims 45-67 of copending Application No. 10/453,574, Kranzler et al. (US Pat. 6,602,911), Tsuruta et al. (Abstract), Bonnaud et al. and Hirsh et al. (US Pat. App. Pub. 2004/0122104) are cited for the same reasons as above and are incorporated herein to avoid repetition.

The difference between the claims of said copending application and the claims of the present Application is that the claims of said copending application do not expressly claim the use of a metabolite. However, the prior art amply suggests the same as the prior art indicates that active metabolites of milnacipran may be used to treat various diseases and conditions, such as depression. As such, one of ordinary skill in the art would expect that metabolites, such as F2782 and F2800, would be effective in the treatment depression and other conditions or diseases.

Therefore, the claimed invention, as a whole, would have been an obvious modification of the claims of said copending application to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references and claims of said copending application.

The above are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

FIC
February 3, 2005

JOHN PAK
PRIMARY EXAMINER
GROUP 1600